Ethical Conflicts in Randomized Controlled Trials

Robert D. Truog, MD

Professor of Medical Ethics, Anaesthesia & Pediatrics, Harvard Medical School

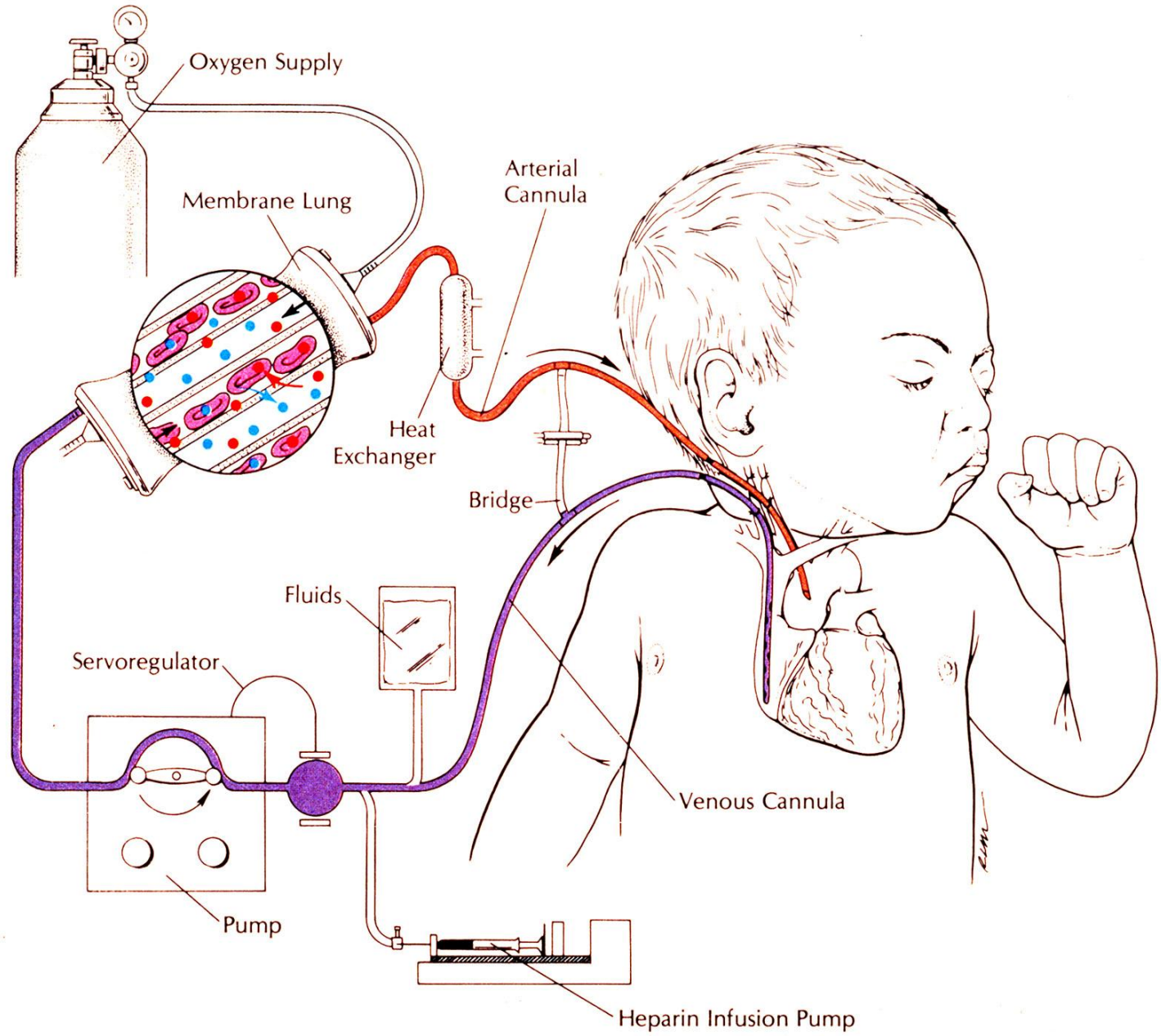
Overview

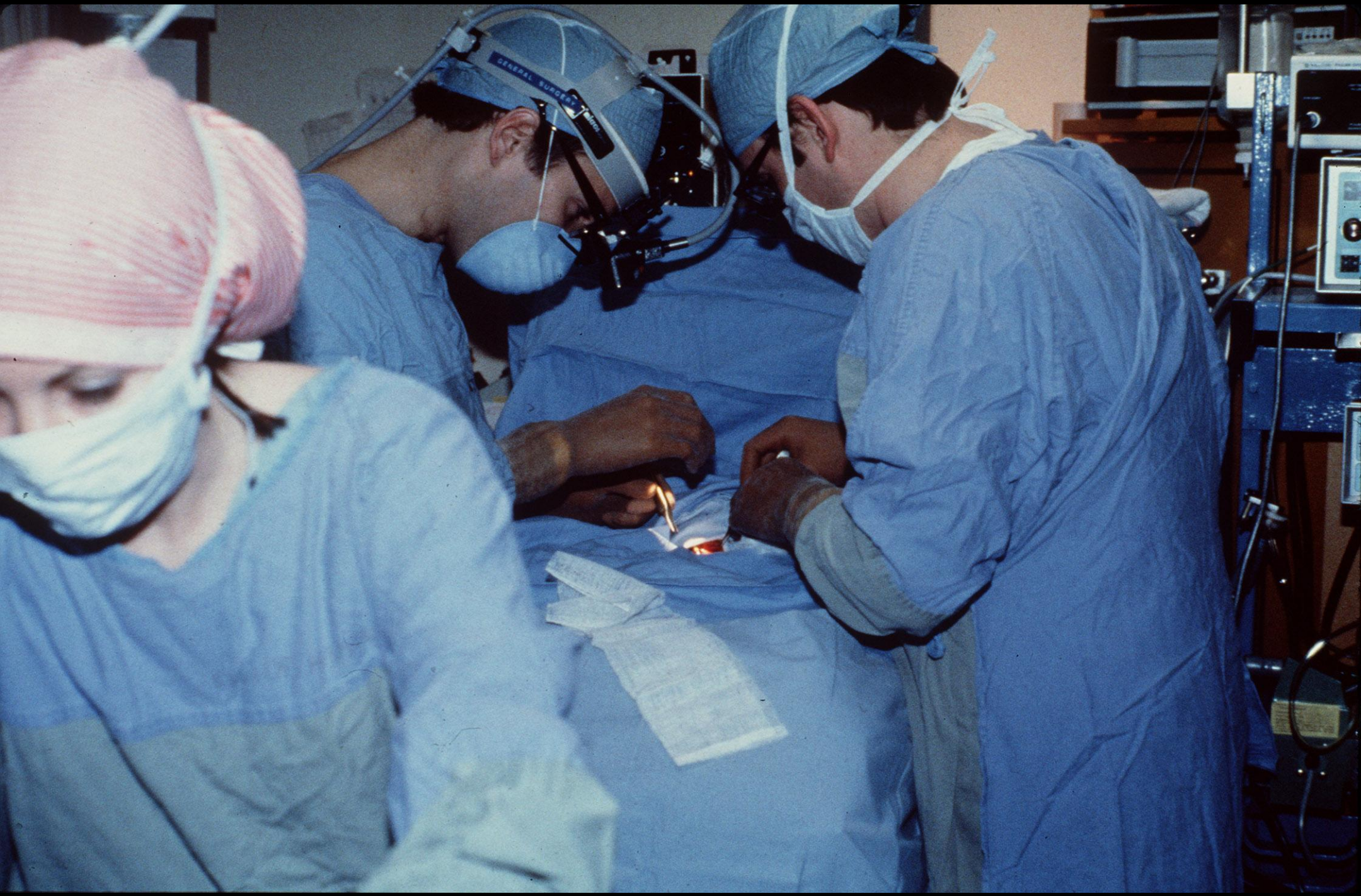
- ExtraCorporeal Membrane Oxygenation (ECMO):
  - A Case Study
- Clinician vs Investigator:
  - The Fundamental Conflict
- Adaptive Randomization:
  - Balancing Conflicting Obligations
- Randomized Consent (Zelen Randomization):
  - Easing the Psychological Burdens
- Are RCTs the only way to learn?
  - Ethical boundaries vs statistical certainty

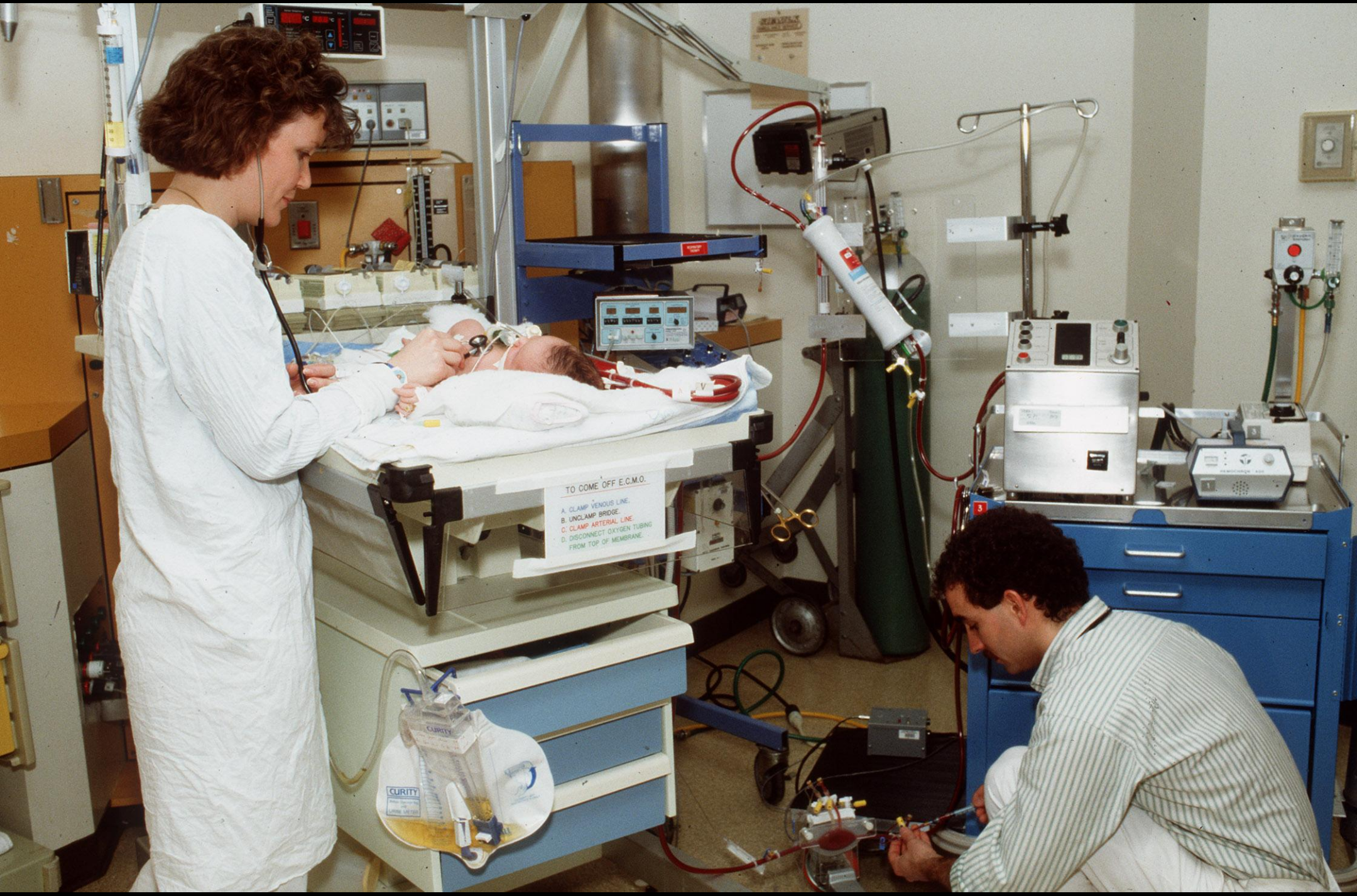
Extracorporeal Membrane Oxygenation and Conventional Medical Therapy in Neonates With Persistent Pulmonary Hypertension of the Newborn: A Prospective Randomized Study

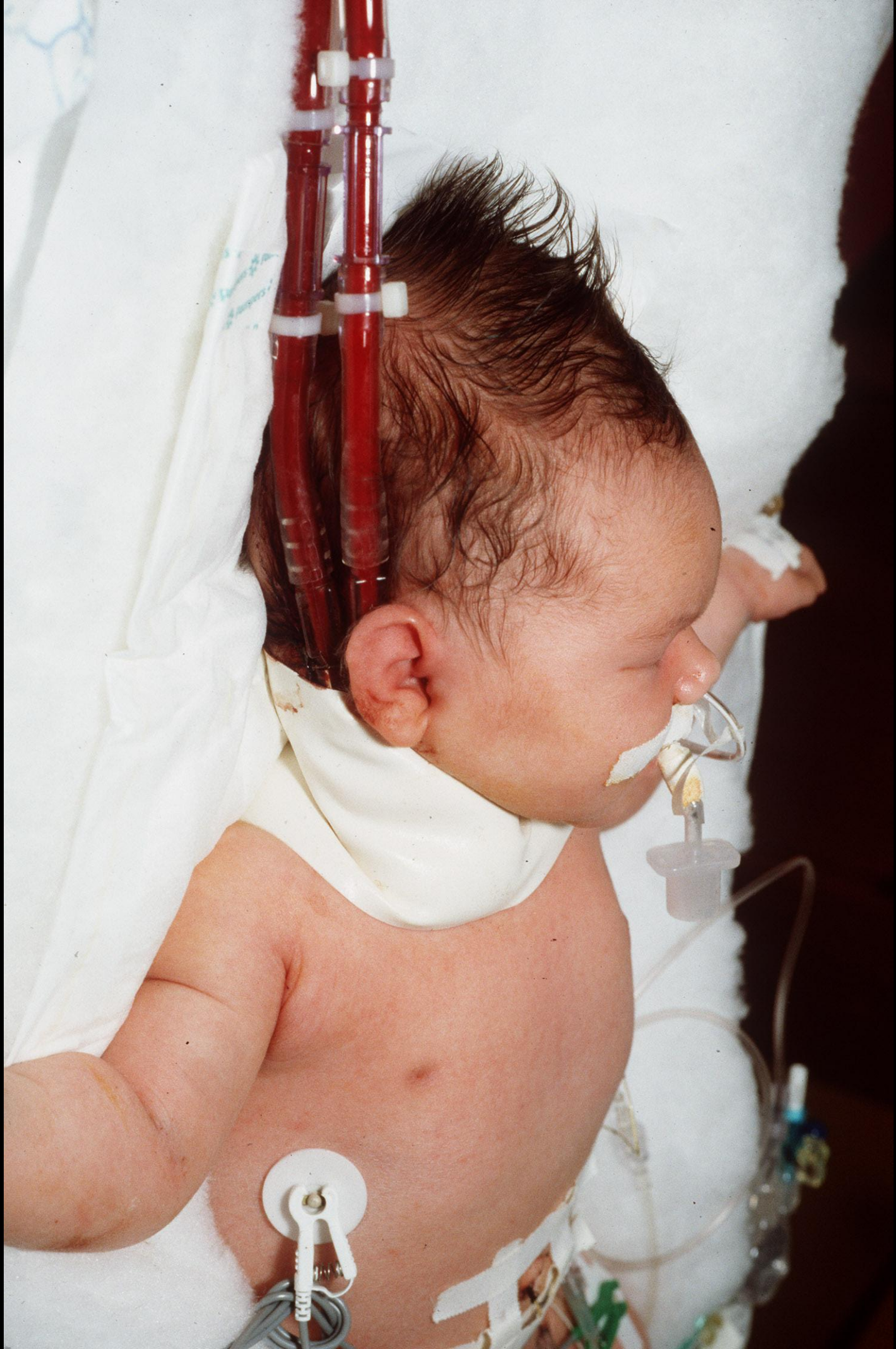
P. Pearl O'Rourke, MD, Robert K. Crone, MD, Joseph P. Vacanti, MD, James H. Ware, PhD, Craig W. Lillehei, MD, Richard B. Parad, MD, and Michael F. Epstein, MD

From the Departments of Anesthesia, Surgery, and Newborn Medicine of the Children's Hospital, Harvard Medical School, and the Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts


Oxygen Supply
Membrane Lung
Arterial Cannula
Heat Exchanger
Bridge
Fluids
Servoregulator
Venous Cannula
Pump
Heparin Infusion Pump


GENERAL SURGERY


TO COME OFF E.C.M.O.
A. CLAMP VENOUS LINE.
B. UNCLAMP BRIDGE.
C. CLAMP ARTERIAL LINE.
D. DISCONNECT OXYGEN TUBING FROM TOP OF MEMBRANE.
CURITY
CURITY



Background to the Harvard Trial

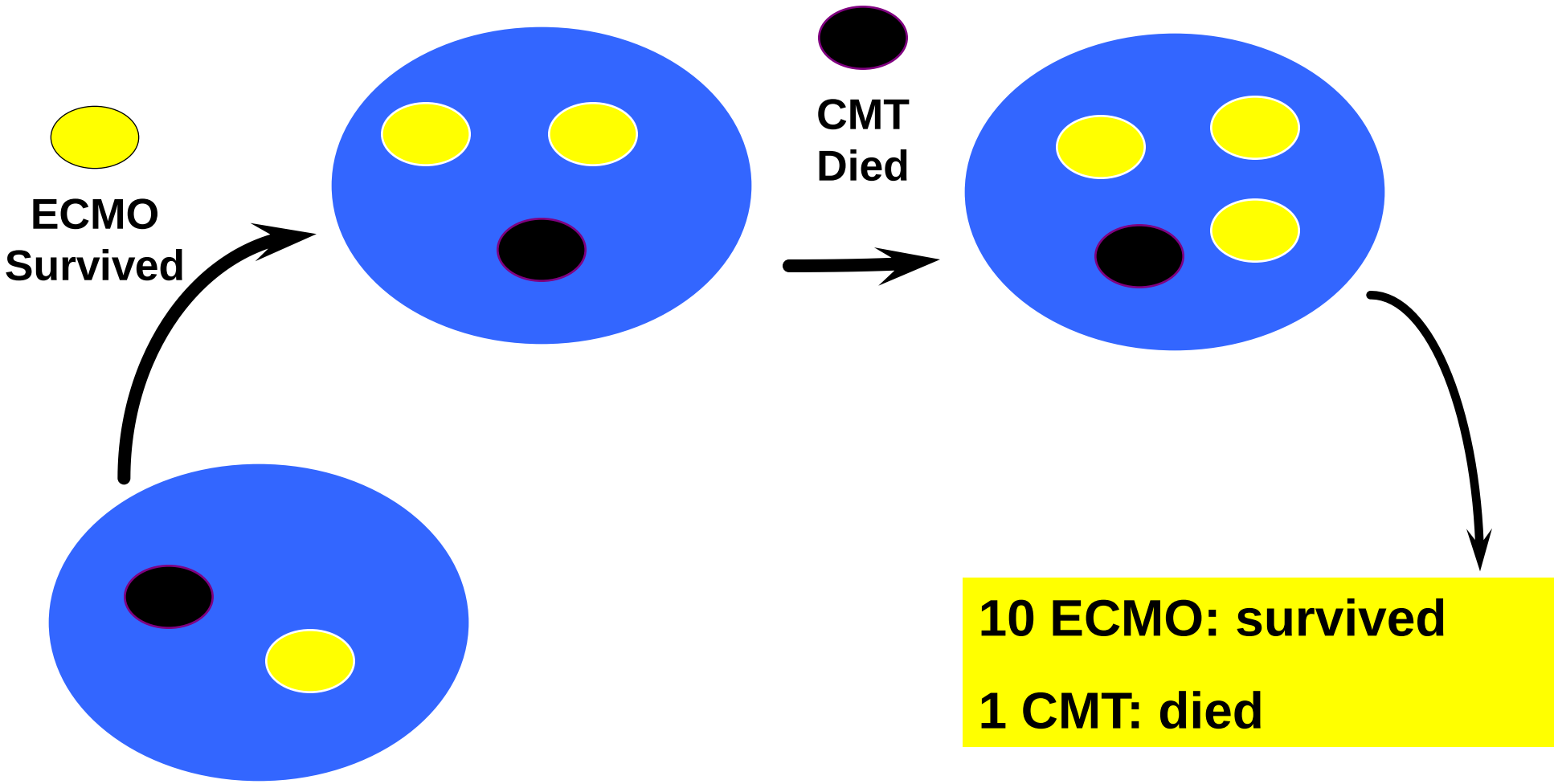
- An RCT in the 1970s had shown ECMO not effective for ARDS in adults
- In the 1980s, Robert Bartlett used ECMO to treat newborns with PPHN
- Results were very impressive
- But, pediatricians were reluctant to adopt ECMO without convincing data from an RCT

Pediatrics

Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective Randomized Study

Robert H. Bartlett, MD, Dietrich W. Roloff, MD, Richard G. Cornell, PhD, Alice French Andrews, MD, Peter W. Dillon, MD, and Joseph B. Zwischenberger, MD

Bartlett: Play-the-Winner Design



Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective Randomized Study

JAMES H. WARE and MICHAEL F. EPSTEIN

Pediatrics 1985;76;849-851

"The clinical indications for this new and complex treatment remain undefined. Further randomized controlled trials… will be difficult but remain necessary."

Extracorporeal Membrane Oxygenation and Conventional Medical Therapy in Neonates With Persistent Pulmonary Hypertension of the Newborn: A Prospective Randomized Study

P. Pearl O'Rourke, MD, Robert K. Crone, MD, Joseph P. Vacanti, MD, James H. Ware, PhD, Craig W. Lillehei, MD, Richard B. Parad, MD, and Michael F. Epstein, MD

From the Departments of Anesthesia, Surgery, and Newborn Medicine of the Children's Hospital, Harvard Medical School, and the Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts

The Harvard Neonatal ECMO Trial

Randomized newborns with PPHN to conventional therapy versus ECMO

Conventional Therapy

NICU: 7th Floor

Neonatologists

No patients had ever been offered ECMO

Anti-ECMO

ECMO

PICU: 5th Floor

Anesthesiologists & Surgeons

Already had experience with ECMO for newborns with CDH

Pro-ECMO

The Harvard Neonatal ECMO Trial:Study Design

- Eligible newborns had PPHN and a predicted mortality of 85% based upon retrospective data
- Phase I: 50/50 randomization until 4 deaths in one arm
- Phase II: Assign all pts to the more successful therapy, until 4 deaths in that arm or until statistical significance achieved
- Seek consent only from those randomized to the experimental therapy (ECMO)

$$P(p_1 > p_2) = \frac{F_1}{F_1 + F_2 + F_3},$$

$$P(p_1 = p_2) = \frac{F_2}{F_1 + F_2 + F_3},$$

$$P(p_1 < p_2) = \frac{F_3}{F_1 + F_2 + F_3},$$

where

$$\begin{aligned} F_1 &= \int_0^1 \int_0^{p_1} p_1^{a-2}(1-p_1)^{b-1} p_1^6 (1-p_1)^4 p_2^9 \, dp_1 \, dp_2 \\ &= \int_0^1 p_1^{a+4}(1-p_1)^{b+3} \int_0^{p_1} p_2^9 \, dp_1 \, dp_2 \\ &= \frac{1}{10} \int_0^1 p_1^{a+14}(1-p_1)^{b+3} \, dp_1 \\ &= \frac{1}{10} \frac{\Gamma(a+15)\Gamma(b+4)}{\Gamma(a+b+19)} \end{aligned}$$

and, similarly

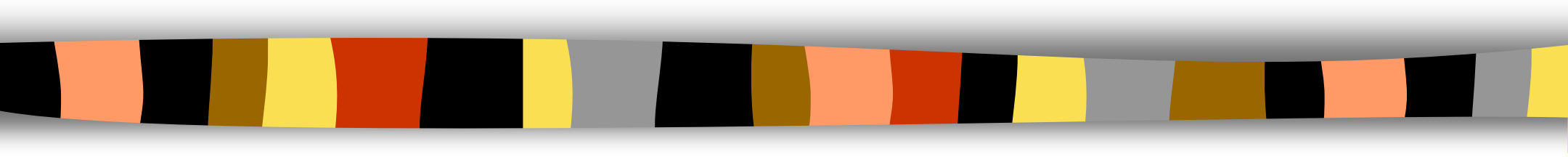
$$F_2 = \frac{\Gamma(a+15)\Gamma(b+4)}{\Gamma(a+b+19)},$$

$$F_3 = \frac{1}{10}\left[\frac{\Gamma(a+6)\Gamma(b+3)}{\Gamma(a+b+9)} - \frac{\Gamma(a+16)\Gamma(b+3)}{\Gamma(a+b+19)}\right].$$

The Harvard Neonatal ECMO Trial: Results

	ECMO	CMT
Phase I	**9 s, 0 d**	**6 s, 4 d**
Phase II	**19 s, 1 d**	

Healer versus Investigator



The Fundamental Conflict

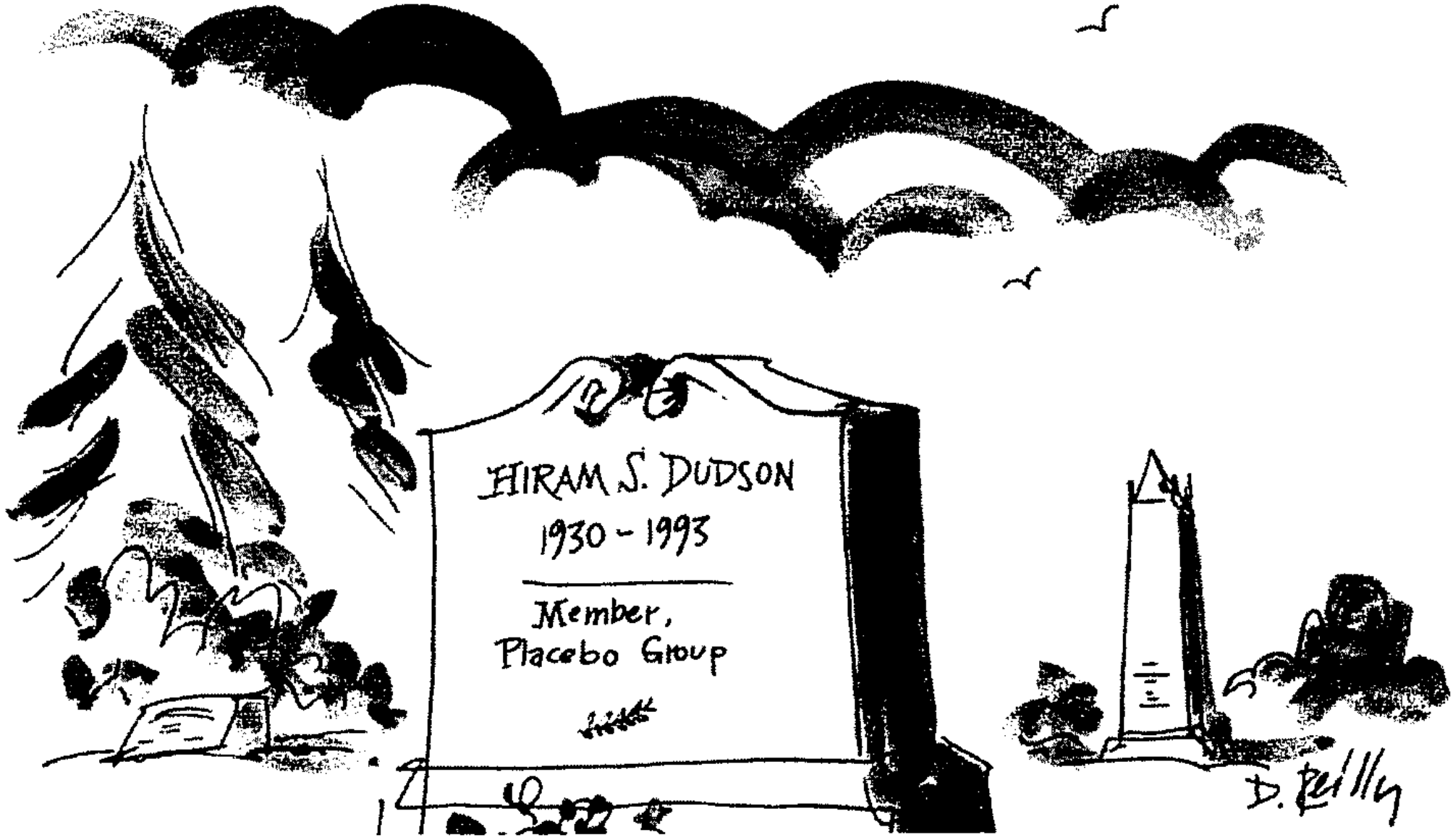
Two views of medical research

- The “difference position” (scientific perspective)
  - Clinical trials are scientific experiments governed by the requirements of good science
- The “similarity position” (clinical perspective)
  - Clinical trials are intended as beneficial therapy governed by the ethics of the doctor / patient relationship

The fundamental dilemma

- A dilemma confronts physician-investigators…
- As physicians they are dedicated to caring for their patients…
- As investigators they are dedicated to caring for their research…
- These two commitments conflict whenever an individual physician/investigator comes face to face with an individual patient/subject.

Jay Katz, 1993


HIRAM S. DUDSON
1930 - 1993
Member,
Placebo Group
D. Reilly

The Difference Position

"Researchers must give patients stark, bold, and dramatic signs that research is different from clinical care… instead of the white coats associated with medical care, investigators could wear red ones…"

Dresser R. Soc Philos Policy 2002; 19:271

The Difference Position

"This morning I was your doctor and you were my patient, but this afternoon I am going to be giving you an experimental medication, and then I am no longer your doctor, but an investigator, and you are my subject. During this time you need to know that I will place the pursuit of scientific knowledge above your interests, and will no longer be providing you with individualized care."

Truog RD. Intensive Care Med 2005;31:338

Similarity position #1: Personal Equipoise

- Requires that the investigator be personally unbiased between the treatment arms, “perfectly balanced on the edge of the sword”
- But, researchers usually “believe in” the treatments they study
- Requiring personal equipoise leaves investigators feeling either “guilty” or “cynical”

Similarity Position #2: Clinical Equipoise

- Requires uncertainty within the medical community as a whole
  - "I believe that "A" is better, but if your appointment had been with my colleague down the hall, she would have recommended "B"
  - "So… would you agree to have your treatment determined by a coin flip, so that we can learn from this experience?"

Freedman B. N Engl J Med 1987;317:141

Healer versus Investigator: The Fundamental Conflict

- “Physicians traditionally act in the best interests of each patient under their care, and patients expect this of their physician.

- If this commitment to the patient is attenuated, even for so good a cause as benefits to future patients, the implicit assumptions of the doctor-patient relationship are violated.

- I have no doubt that we would lose more than we would gain by adopting such an approach.“

Angell, NEJM, 1984

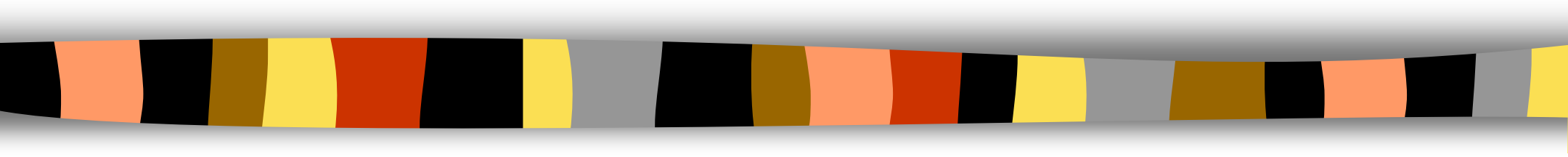
What's the solution to this fundamental conflict?

- "What can be done when non-randomized designs are considered inadequate but randomization would be difficult…?"

- "Not all problems have solutions."

Angell, NEJM, 1984

Adaptive Randomization



Balancing Conflicting Obligations

Adaptive Randomization

- Definition: Deviating from “balanced” or 50/50 randomization, with more patients assigned to the therapy that is “leading” during the trial

- Betting on the horse who is out in front, before we know how the race will end

Adaptive Randomization: Advantages

- Attempts to mitigate the conflict of healer versus investigator
- Attempts to minimize number of patients assigned to the less-successful therapy
  - In the Bartlett trial, 50/50 randomization was guaranteed only for the first patient
  - In the Harvard trial, 50/50 randomization was guaranteed until the 4th death in one arm

Adaptive Randomization

- In the literature, the trial was criticized from both directions
  - No patients should have been assigned to CMT
  - Not enough patients were assigned to CMT

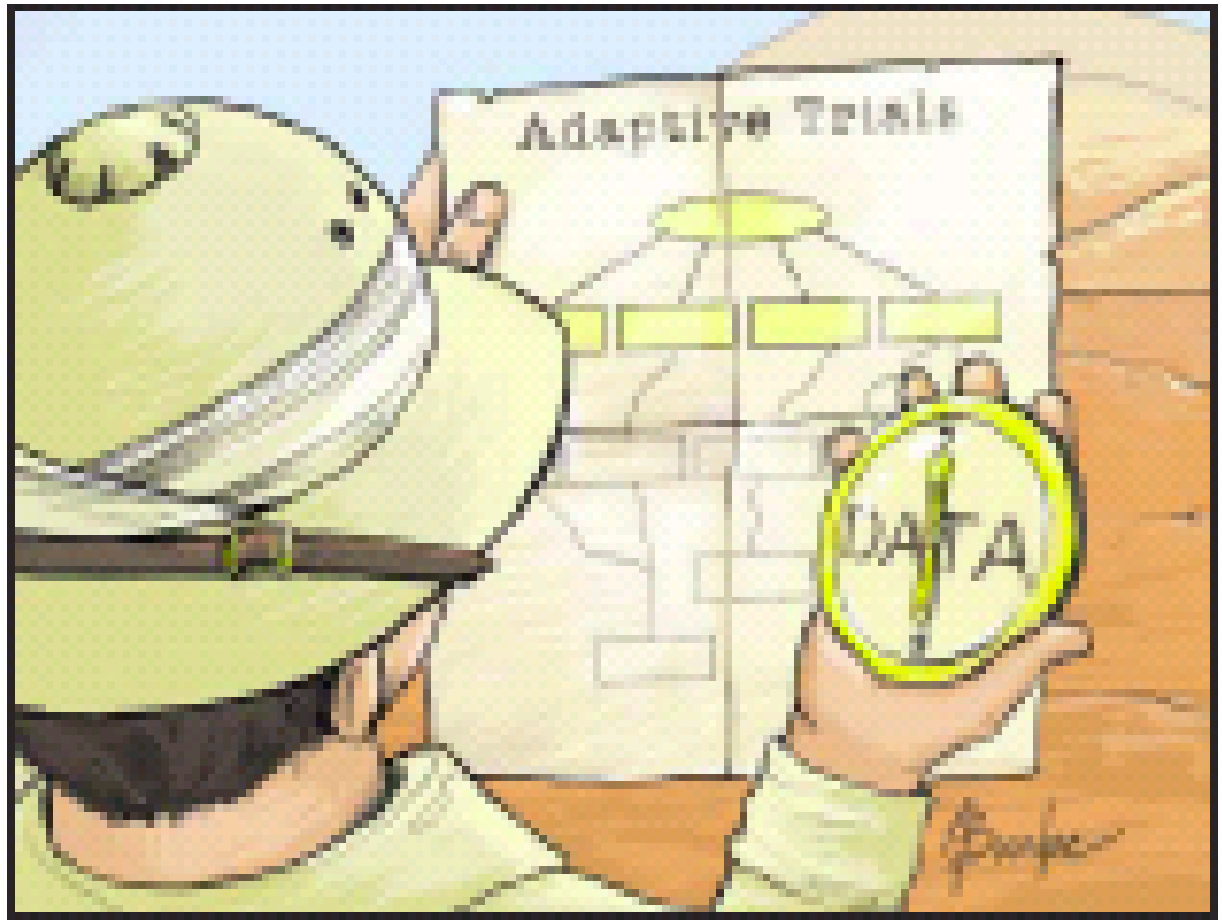
- Perhaps this approach was a good balance

Adaptive Randomization

Adaptive methods should be used as a matter of course. It never pays to commit oneself to a protocol under which information available before the study or obtained during its course is ignored in the treatment of a patient.

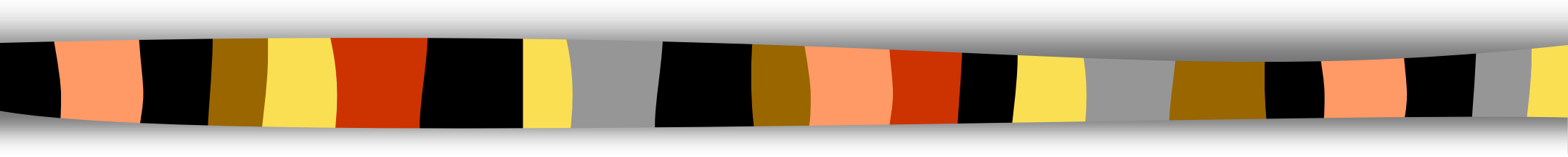
Weinstein, NEJM, 1974

Industry, FDA Warm to "Adaptive" Trials



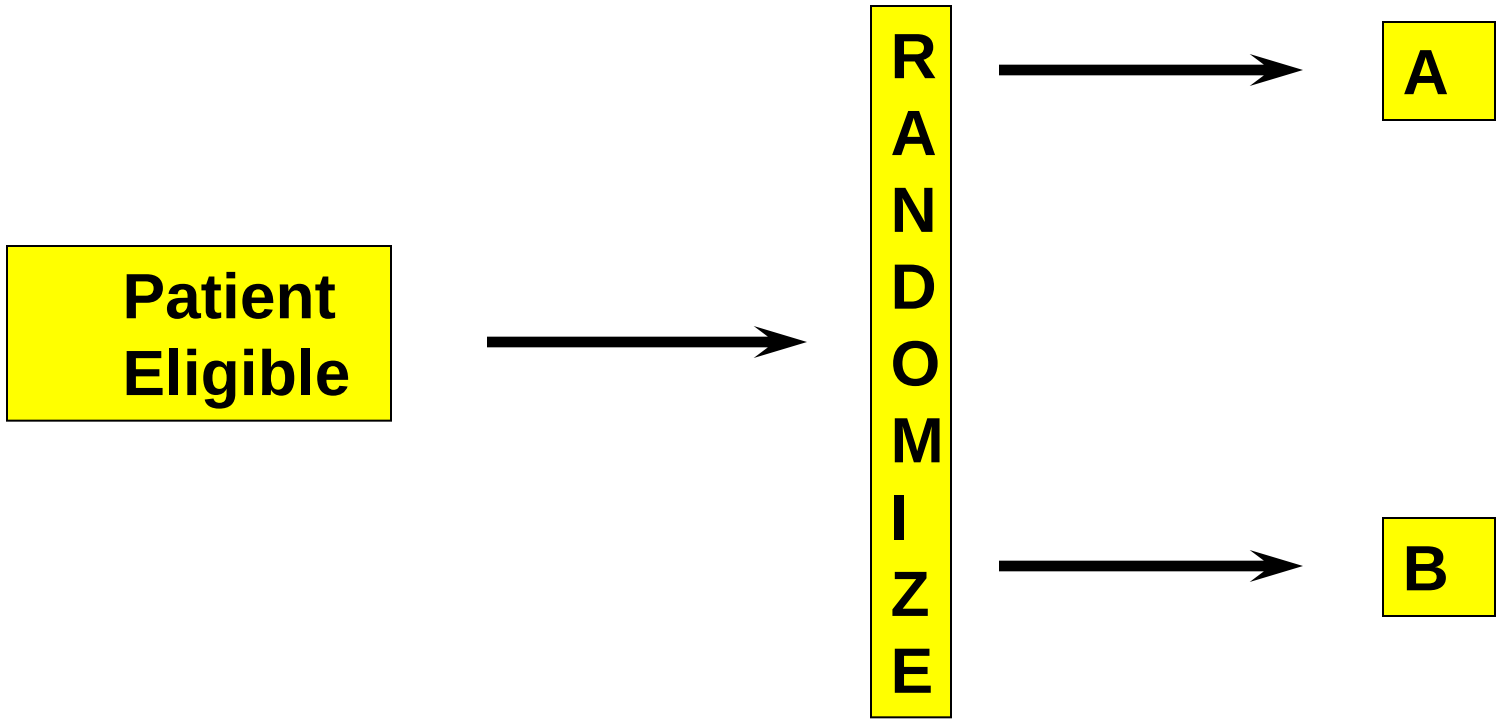
Kuehn BM. JAMA 2006; 296(16):1955-1957.

Randomized Consent (Zelen Randomization)

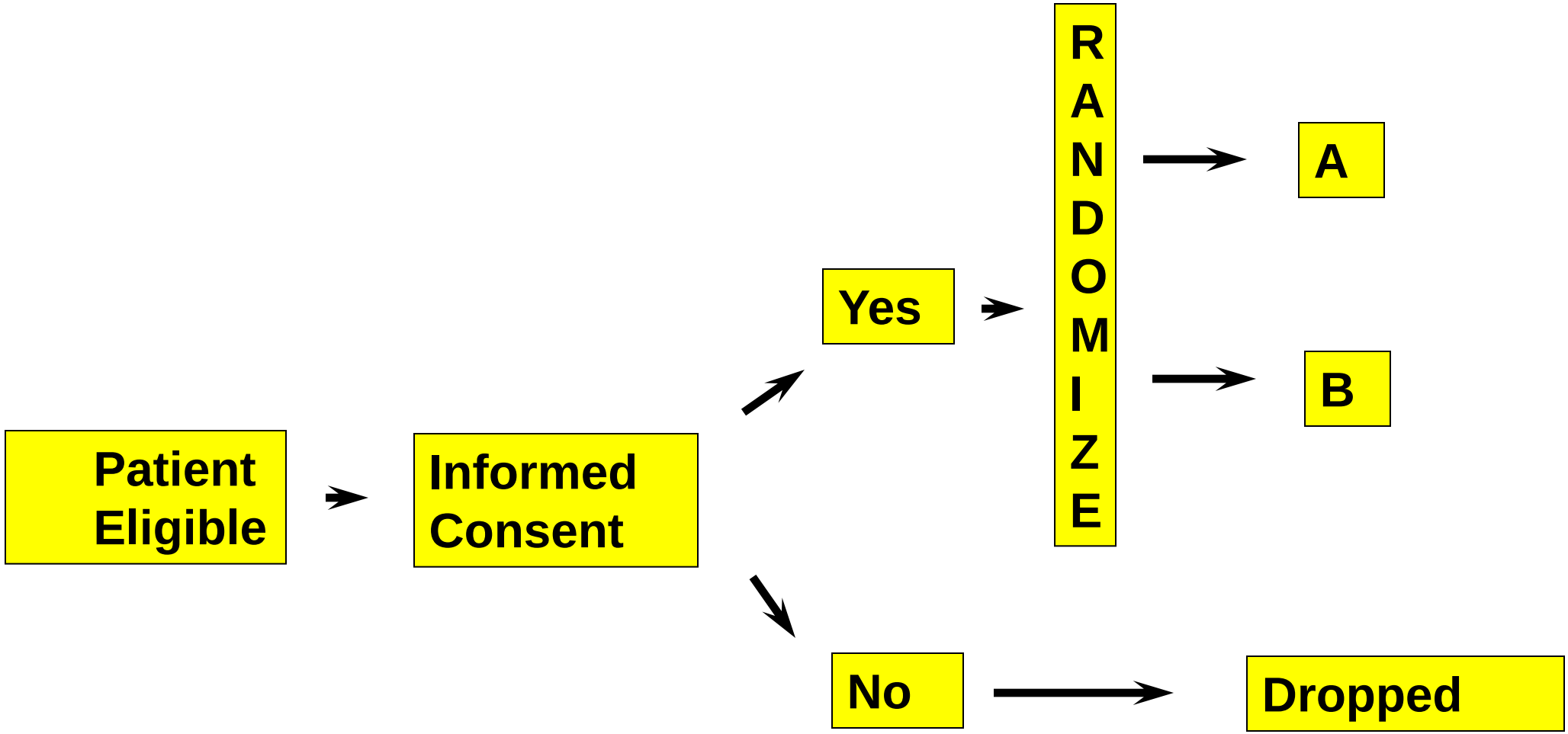


Easing the Psychological Burdens

Conventional RCT, Without Informed Consent



Conventional RCT, With Informed Consent



SPECIAL ARTICLE ARCHIVE

A New Design for Randomized Clinical Trials

Marvin Zelen, Ph.D.

N Engl J Med 1979; 300:1242-1245 | May 31, 1979

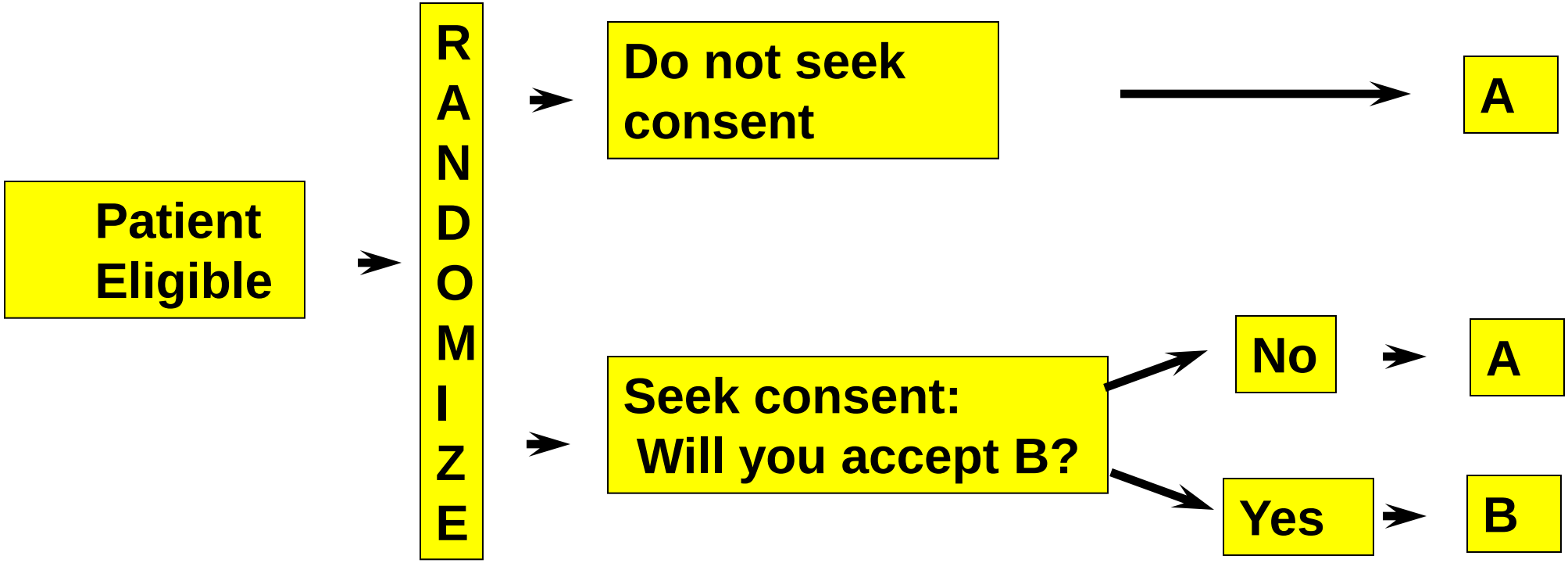
Marvin Zelen

Lemuel Shattuck Research Professor of Statistical Science and Member of the Faculty of Arts and Sciences

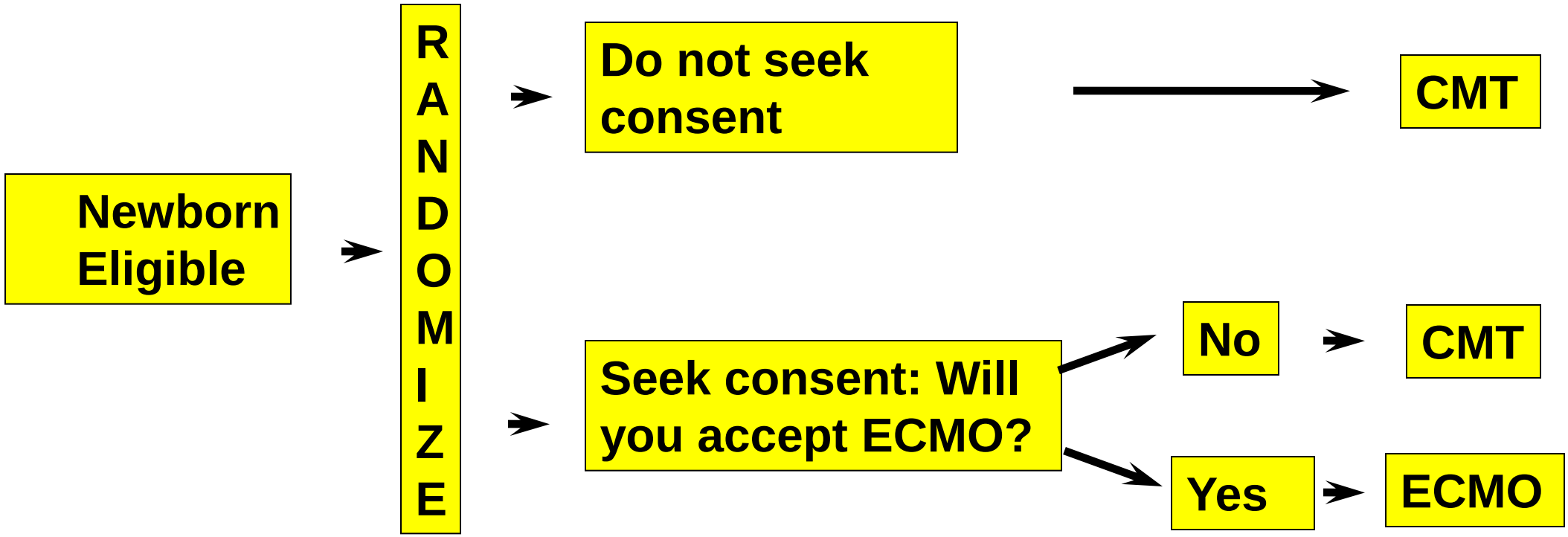
Department of Biostatistics

Harvard School of Public Health

Randomized Consent



Randomized Consent



Question

- Is this approach to informed consent ethical?

The ECMO Trial: Justifications for Randomized Consent

- Control patients were not really research subjects
- Parents of control patients were not really being offered a choice, so why subject them to stress?
- Pressure to cross-over from CMT to ECMO would have been unbearable

The Response to the ECMO Trial

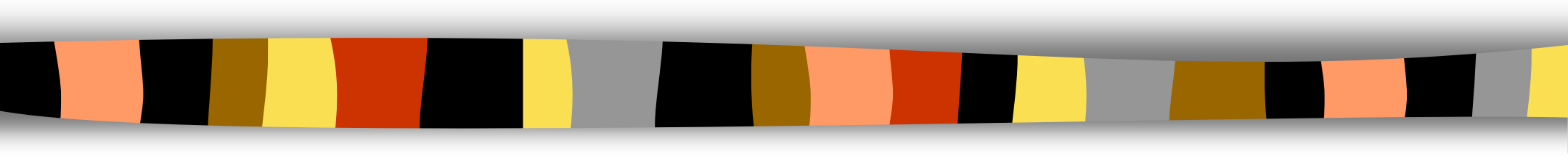
- The NIH Office for Protection from Research Risks (OPRR) reprimanded the hospital

- The hospital IRB “made decisions that rightfully belonged to the parents. They really blew it.”

  Charles McCarthy, Director of OPRR

- The doctors “were doing exactly what physicians did before we had a doctrine of informed consent - making decisions for parents.” George Annas, Boston University

Are RCTs the only way to learn?



Approaches to Learning: Ascending Order of Confidence

- Meta-analyses
- Randomized Controlled Trials
- Case / Control Observational Studies
- Databases
- Case Series with Historical Controls
- Case Series with Literature Controls
- Case Series without Controls
- Anecdotal Case Reports

Are RCTs the only way to learn?

- “The brilliant success of the RCT has now become a form of intellectual tyranny” *Freireich*

- “We should not proceed on the fallacious assumption that where there is no randomization, there is no truth.” *Royall*

Are RCTs the only way to learn?

"The difference between the RCT and the observational, retrospective study is not the difference between good and bad science, truth or falsity, but a difference between varying degrees of confidence." *Fried*

The New England Journal of Medicine

Special Articles

A COMPARISON OF OBSERVATIONAL STUDIES AND RANDOMIZED, CONTROLLED TRIALS

KJELL BENSON, B.A., AND ARTHUR J. HARTZ, M.D., PH.D.

Conclusions

We found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in randomized, controlled trials. (N Engl J Med 2000;342:1878-86.)

We should abandon randomized controlled trials in the intensive care unit

Jean-Louis Vincent, MD, PhD, FCCM

The randomized controlled trial is seen by many as the summit of evidence-based medicine, yet, in the intensive care unit, randomized controlled trials can be challenging to conduct, and results are often difficult to interpret and apply. Many randomized controlled trials in intensive care patients have not demonstrated beneficial effects of the intervention under investigation often despite good preclinical and even previous randomized controlled trial evidence. There are many reasons for these negative results including problems with timing, end point selection, and heterogeneous populations. In this article, we will discuss the limitations of randomized controlled trials in the intensive care unit population and highlight the importance of considering other study designs in the challenging intensive care unit environment.
(Crit Care Med 2010; 38[Suppl.]:S534–S538)

“I will argue that in many situations with the ICU context, the RCT as we know it should be abandoned, at least temporarily, and much greater emphasis be placed on gathering information from well-designed observational studies.”

When should we think about alternatives to the RCT?

- When evaluating potentially life-saving therapies
  - Subjects do not “choose” to enroll, but are chosen by their disease - relationship is fiduciary, not contractual
  - Only 35% of physician investigators say they strictly adhere to the protocol in these situations
  - If the patient deteriorates, many say they seek to alter the protocol or seek compassionate use of the experimental treatment

Morris, Crit Care Med 2000, 28:1156

When should we think about alternatives to the RCT?

- When evaluating rapidly developing technologies
  - Improvements in both experimental and control treatments may make the results of the RCT obsolete by the time it is published

When should we think about alternatives to the RCT?

- When RCTs are not the most efficient way to acquire knowledge
  - ARDSNet tidal volume study - $15 million
  - Confirmed a secular trend that was already occurring based on non-randomized data
  - Only one of multiple permutations of vent management

When should we think about alternatives to the RCT?

- When the non-randomized data are compelling...

- 1988: Database on 715 newborns treated with ECMO (Toomasian et al)
  - 81% survival
  - Statistically superior to any treatment with survival rate < 78.4%

Questions

- Given these data…
  - Was the Bartlett trial necessary? Was it ethical?
  - Was the Harvard trial necessary? Was it ethical?

- Given all you've seen, are you convinced that ECMO is superior to conventional therapy?

The UK Neonatal ECMO Trial

- Field et al. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. Lancet 1996;348:75-82.
- The existing “RCTs of neonatal ECMO… suggested reductions in mortality but were not conclusive.”
- “used adaptive designs, which may have introduced bias…”

The UK Neonatal ECMO Trial

- 1993-1995: 185 neonates randomized to ECMO vs CMT
- Trial stopped early by DSMB,
  - ECMO survival 60/93 = 65%
  - CMT survival 38/92 = 41%, $p<0.0005$
- Were 22 babies unnecessarily “sacrificed”?

Conclusions

- The conflict between clinician and investigator is profound and can never be entirely eliminated
- Adaptive randomization is one way to balance the competing obligations
- Zelen randomization reduces the psychological burdens of the investigators, but is probably ethically unacceptable

Conclusions

- RCTs are usually the best approach for evaluating new therapies
- Alternatives to RCTs should be considered:
  - when therapies are potentially life-saving
  - when the technologies are developing rapidly
  - when RCTs are not the most efficient method
  - when non-randomized data are compelling
- Investigators, journal editors, and granting agencies will have to reconsider their blind insistence upon RCTs for this to occur

Conclusions

"The use of statistics in medical research has been compared to a religion: it has its high priests (statisticians), supplicants (journal editors and researchers), and orthodoxy (for example, $p<.05$ is "significant")"

Benjamin Freedman

“Never, ever, think outside the box”